3. DOWN'S SYNDROME (A)

Down's syndrome is probably the most common of the severe developmental disorders which permit survival after birth. There may be a million affected individuals in the world at the present time. Since the discovery (Lejeune et al., 1959) that the condition was associated with the presence of an extra small acrocentric chromosome, conventionally termed No. 21, there has been renewed interest in all aspects of the condition.

It has been known for many years that the frequency is greater in older mothers and that the condition occurs all over the world, probably in people of all ethnic origins. The mortality in childhood is very high, and it is likely that about half of those born alive die by 10 years of age. This mortality is not restricted to affected children who have associated congenital heart disease.

There are few reliable estimates of frequencies in different populations, and most of these relate to European or North American populations. Such estimates have to be expressed either as birth frequencies standardized for maternal age or, in view of the high early mortality, in terms of age-specific prevalence. Unless careful clinical examinations are carried out in the newborn and these are supplemented by dermatoglyphic and chromosome studies, data on birth frequencies have to be interpreted with caution.

There is no doubt that the condition is detectable on superficial examination much less readily in some ethnic groups than in others. In dark-skinned races affected babies are usually rather light in colour, and the so-called " mongoloid slant " of the eyes and epicanthic folds are most readily detectable in occidental peoples. Nevertheless, even experienced physicians and geneticists often have difficulty in making a diagnosis even in European infants unless dermatoglyphic and chromosomal analyses can be undertaken. Over most of Europe the frequency at birth appears to be between 1 and 2 per 1000 total births, but the extremes of the range of frequencies have not been defined.

DATA FROM THE STUDY: FREQUENCIES

Table 3.1 sets out the data from single births reported in the study. All cases have been included even where the record indicated some doubt about the diagnosis. There is no clear evidence that pregnancy is unduly disturbed or characterized in any way when the child *in utero* has Down's syndrome; however, hospital series will reflect the priority for admission given to elderly and multiparous women. We know that it is maternal age rather than parity that is associated with the syndrome and therefore the frequencies of the condition set out in Table 3.1 have been standardized for maternal age.

Differences in the standardized frequencies in Table 3.1 could (*a*) be due to sampling fluctuations, (*b*) reflect differences in standards of recognition in the centres, or (*c*) reflect real frequency differences in populations. Factors (*a*) and (*b*) are probably of such importance that we cannot judge from the data whether there are any real differences in frequencies in the different centres. Our own clinical experience and experience in special investigations over a range of hospitals elsewhere indicate that as many as a quarter of all children with Down's syndrome may not be recognized until after the child has left hospital. However, the standard of diagnosis is probably improving as dermatoglyphic and chromosomal analyses are more generally available and used.

As will be seen from the tables the numbers of cases in most centres are small and the sampling fluctuations are presumably correspondingly large. It is comforting to note the very different frequencies, even after standardization for maternal age, in the two Melbourne hospitals which had some staff in common and would be expected to maintain similar diagnostic standards.

It is of interest that no cases were reported from Alexandria or from the two centres in India, Bombay and Calcutta. There were no cases in the 4141 births to Indian mothers in Kuala Lumpur and only one affected child born to the 3119 Indian mothers in Singapore, so that in all there was only one reported case born to nearly 66 000 Indian mothers.

It may be noted that the frequencies of all neural tube defects (B1-B7) and that of Down's syndrome (both standardized for maternal age) are not correlated ($r = 0.139$).

The relatively high frequency in Mexico was all in *mestizos* (Spanish-Amerindians) but they consti-

tuted over 98% of births. The only data on the offspring of Amerindian mothers are from Santiago, where 3 affected infants were born to 494 such mothers. It will be noted from Table 3.1 that the frequencies in Hong Kong, Kuala Lumpur and Singapore were very low. Subsequent conversations or correspondence with the organizers in four of the above centres made it clear that cases are seen relatively commonly by paediatricians and that it was quite possible that owing to specific difficulties cases may have been missed at birth.

EFFECTS OF MATERNAL AGE

Maternal age no doubt influences the frequency of this syndrome in offspring everywhere but the maternal-age/frequency relationship is not necessarily the same in different parts of the world. It follows that the data must be interpreted with caution. The relationship that emerges is nevertheless of some interest, and is not dissimilar to that derived from published series, mostly of older living affected children, reported from Europe and North America.

Of the 347 cases of Down's syndrome recognized, 176 were born to mothers over 35 years of age, although they constituted less than 11% of all mothers, and as may be seen from the following tabulation, the pattern of frequency at birth to mothers at different maternal ages is similar to that in other published series; these figures show the frequency per 1000 total single births of children with Down's syndrome born to mothers in the age-group shown:

<15 years	*15-19 years*	*20-24 years*	*25-29 years*	*30-34 years*	*35-39 years*	*40-44 years*	*>45 years*
0.30	0.50	0.32	0.38	1.63	2.11	6.34	16.65

SEX PROPORTION (M/M+F)

In the reported cases the sex proportion is 0.45. In series of cases based on older children, an excess of males has been reported (Penrose, 1963; Glancy, 1958). In the few births series published, as in the present data, there does not appear to be such an excess, suggesting a relatively greater early mortality in females. Of the 40 cases which were stillborn or died in this study 28 were female.

DOWN'S SYNDROME IN MULTIPLE BIRTHS

Eleven cases of Down's syndrome occurred in multiple births. The female was affected and the males normal in one MMF set of triplets. In one MM pair, one had Down's syndrome and the other was represented only by a trunk and legs. In one FF pair, one had anencephalus and the other Down's syndrome. In two MM and two FF pairs one had Down's syndrome and the other was normal. The male was normal and the female had Down's syndrome in three MF pairs, and the male was affected and the female normal in another.

TABLE 3.1
DOWN'S SYNDROME (A) IN SINGLE BIRTHS

CENTRE		Number of cases			Mean maternal age		Frequencies standardized for maternal age per 1000 total births
		M	F	T	Down's syndrome	All not malformed	
I 1	MELBOURNE	3	5	8	27.5	26.3	0.93
I 2	MELBOURNE	3	3	6	38.3	26.3	2.09
II	SAO PAULO	7	4	11	34.8	26.4	0.86
III	SANTIAGO	14	23	37	34.4	27.6	1.34
IV 1	BOGOTA	6	4	10	34.5	25.9	0.57
IV 2	MEDELLIN	9	9	18	31.7	27.7	0.81
V	CZECHOSLOVAKIA	15	12	27	30.1	25.5	2.02
VI	ALEXANDRIA	0	0	0	-	28.1	0.00
VII	HONG KONG	0	1	1	22.5	29.9	0.17
VIII 1	BOMBAY	0	0	0	-	26.8	0.00
VIII 2	CALCUTTA	0	0	0	-	25.6	0.00
IX 1	KUALA LUMPUR	1	2	3	35.8	28.2	0.16
IX 2	SINGAPORE	6	11	17	35.1	28.1	0.37
X 1	MEXICO CITY	21	25	46	33.3	27.6	1.97
X 2	MEXICO CITY	10	12	22	34.3	27.3	1.72
XI	BELFAST	11	17	28	35.7	27.8	1.07
XII	PANAMA CITY	6	11	17	31.9	25.1	1.44
XIII	MANILA	8	9	17	35.1	27.6	0.54
XIV 1	CAPE TOWN	0	0	0	-	27.2	0.00
XIV 2	JOHANNESBURG	5	3	8	31.9	25.6	0.83
XIV 3	PRETORIA	2	4	6	34.2	26.8	0.59
XV	MADRID	15	24	39	36.3	29.6	1.75
XVI 1	LJUBLJANA	10	10	20	35.5	27.5	3.89
XVI 2	ZAGREB	3	3	6	35.0	26.3	2.47
	TOTAL	155	192	347	34.0	27.3	0.83